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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/635,370	08/09/00	RUBIN L	ONV-060.02

028120
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HM12/0730

EXAMINER	
DAVIS, K	
ART UNIT	**PAPER NUMBER**
1636	10

DATE MAILED: 07/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/635,370	Applicant(s) RUBIN ET AL.	
	Examiner Katharine F. Davis	Art Unit 1636	

-- The MAILING DATE of this communication appears on th cov r sh et with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-78* is/are pending in the application.

4a) Of the above claim(s) *1-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice To Comply* .

DETAILED ACTION

This Office Action is in response to the application filed on August 9, 2000 and to the telephone election of June 7, 2001. Claims 1-78 are pending in the instant application.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-26, 31-47 and 54 drawn to a substantially pure population of viable pancreatic progenitor cells and methods of isolating and differentiating said cells, classified in Class 435, subclass 325.

II. Claims 27-30 and 48-53 drawn to a pharmaceutical composition of a substantially pure population of viable pancreatic progenitor cells and methods of treatment of a subject using said composition, classified in Class 424, subclass 93.1.

III. Claims 55-78, drawn to a method(s) for preparing a substantially pure non-adherent population of progenitor cells, classified in Class 435, subclass 378.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed, a substantially pure population of viable

pancreatic progenitor cells, may be used in a materially different process of using the product such as a tool for study of insulin production *in vitro*, for example.

Inventions I, II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the method(s) of Invention III are not limited to pancreatic progenitor cells therefore the method(s) of Invention III can be practiced with any population of progenitor cells.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their separate classification, separate search requirements and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with David Halstead on June 7, 2001 a provisional election was made with traverse to prosecute the invention of Group III, claims 55-78. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-54 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows: The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications (60/171,338, 60/142,305 and 60/119,576) upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for claims 55-78 of this application. Additionally, Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged. However, the parent application 09/499,362 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 55-78 of this application. The prior cases teach only a method for preparing a substantially pure population of **pancreatic** progenitor cells. The prior cases do not teach any methods for isolation of progenitor cells from any other tissue. Therefore, the prior cases do not provide adequate support for instant claims 55-78.

Specification

The disclosure is objected to because of the following informalities: In the Brief Description of the Drawings each panel or drawing containing multiple panels must be referred to as a separate figure. The first line of each description must refer to each separate figure (*e.g.*, Figures 3A-3G). Correction is required for Figures 3-6, 8 and 46.

Additionally, the Brief Description of the Drawings section contains no descriptions of Figures 41-60.

The specification contains nucleotide and/or amino acid sequences (on page 38) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. Applicant must provide a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office action must include a complete response to the requirement for a new Sequence Listing.

Claim Objections

Claims 62, 67, 68, 70 and 72 are objected to because of the following informalities: Claims 62 and 70 recite the same Markush group members twice; pancreatic tissue in line 2 and pancreas tissue in line 4.

Claim 67 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 55, from which 67 depends, establishes that the claimed progenitor cells are non-adherent cells.

Claim 68 recites the verb "forms" in line 2. The grammatically correct verb is "form".

Claim 70 does not end with a punctuation mark.

Claim 72 appears to contain a Markush group but does not recite the proper Markush language.

Appropriate corrections are required for claims 62, 67, 68, 70 and 72.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 55-78 are drawn to compositions of substantially pure non-adherent populations of progenitor cells and to methods for preparing said progenitor cells.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad in that they encompass compositions of substantially pure non-adherent populations of progenitor cells from any animal organ and/or tissue and methods for preparing said progenitor cells from any animal organ and/or tissue.

The nature of the invention is a method(s) for preparing a population of substantially pure non-adherent progenitor cells.

An analysis of the prior art indicates that it is very difficult to isolate and maintain stem cells in culture (see abstract: Domen *et al.* Molecular Medicine Today 5:201-208 1999;IDS reference). Domen *et al.* state that hematopoietic stem cells are rare cells that cannot be expanded in tissue culture and that can only be isolated in limited numbers as homogenous populations (see page 204, second column, third full paragraph). One of the reasons for this difficulty is that the stem cells undergo apoptosis (see page 203, Hematopoietic stem cells *in*

vitro). The molecular mechanisms behind a stem cell's "choice" to differentiate or undergo apoptosis are unknown. Vogel (Science 290(5497):1672-1674 2000; on-line journal) states that it is not easy to produce viable pure populations of any type of stem cell (see page 4, paragraphs 2-4). Taken together the prior art indicates that the field of stem cell research is in its infancy.

The relative skill of those in the art of molecular biology and tissue culture is high.

The area of the invention is unpredictable. As discussed above, there is a lack of teachings regarding successful isolation and propagation of stem cells in culture. There is no evidence in the art to show that progenitor cells can be identified and/or isolated from any tissue using one protocol. Thus, the effectiveness of a new method for stem cell isolation and propagation from any tissue can not be predicted in the absence of documented success of similar protocols.

The instant specification provides little direction or guidance to support the claimed invention. While the instant specification has taught how to prepare pancreatic progenitor cells and hematopoietic stem cells it has not taught how to prepare non-adherent progenitor cells from any other tissues as recited in claim 62 and/or 70. In order to practice the instant invention in its full scope one of skill in the art would have to know how to disrupt all of the tissues as recited in claim 62 and/or 70 without damaging the cells, how to culture all types of isolated cells, what specific growth factors are useful for each cell type, what quantity of growth factor preparations are effective for each cell type, how to identify the progenitor cells in the culture and how to expand the identified progenitor cell population. Additionally, one of skill in the art would have to know how to culture all tissue-types using a non-adherent protocol. The instant specification is silent with regard to all of these questions.

The working examples disclosed in the instant specification show only the preparation of pancreatic progenitor cells from rats and hematopoietic stem cells from mice and no other preparations of stem cells from any other tissue or any other animal.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the instant specification to teach how to use the claimed method to prepare a substantially pure non-adherent population of progenitor cells from any tissues as recited in claims 62 and/or 70. In order to determine how to use the claimed method to prepare a substantially pure non-adherent population of progenitor cells one of skill in the art would have to be able to rely on well-established successful methods of preparation of non-adherent progenitor cells from any tissue. Since neither the prior art nor the present specification provides the answer to these questions it would require a large quantity of trial and error experimentation by the skilled artisan to answer these questions and successfully use the claimed invention.

Based on the broad scope of the claims, the nature of the invention, the skill of those in the art, the unpredictability of the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to use the claimed method(s) for preparing a substantially pure non-adherent population of progenitor cells from any tissues as recited in claims 62 and/or 70.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73 and 76 are indefinite for the improper use of Markush language. This rejection may be overcome by amending the claims to read (for example) "...the group **consisting of** ..."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 55, 61, 64-69, 71, 74 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Reynolds *et al.* (Science 255(5052):1707-1710 1992). Reynolds *et al.* teach a method for obtaining a population of stem cells from adult mouse striatum (see abstract). The steps of the method of Reynolds *et al.* include enzymatic disruption of the striata of adult mice

and subsequent culture of the striata cells in culture dishes without a substrate (see page 1707, second paragraph). The cell culture media of Reynolds *et al.* includes epidermal growth factor without added adhesion factors (see page 1707, second paragraph). The cells of Reynolds *et al.* are non-adherent, floating cells that form homotypic spheres and are reactive for nestin (see page 1708, column 2, top right). Claims 55, 61, 64-69, 71, 74 and 75 read on the cells and methods of Reynolds *et al.*

Claims 55, 61-70, 73, 74 and 76 rejected under 35 U.S.C. 102(e) as being anticipated by Peck *et al.* (US Patent 6,001,647). Peck *et al.* teach a method of preparing a population of stem cells from a suspension of pancreatic cells isolated from the pancreas of a mammal (see column 8, lines 1-3 and column 18, Example 7). The cell suspension is treated with a growth factor preparation, for example, insulin-like growth factor, epidermal growth factor and/or fibroblast growth factor (see column 8, lines 59-65). The cell suspension of Peck *et al.* is allowed to proliferate to form cell clusters (foci or spheres) which float in the medium (see column 15, lines 6-42). The cell population of Peck *et al.* expresses glucagon and insulin (see column 17, lines 54-58). Peck *et al.* also teach mechanical (reflux pipetting) and enzymatic (trypsin digestion) means of tissue and/or cell culture disruption (see column 17, lines 49-50). Claims 55, 61-70, 73, 74 and 76 read on the cells and methods of Peck *et al.*

Claims 55, 61, 62, 66, 67, 69, 70, 72, 74 and 75 are rejected under 35 U.S.C. 102(e) as being anticipated by Hoffman *et al.* (US Patent 6,241,984 B1). Hoffman *et al.* teach a method of preparing a population of hematopoietic stem cells in a culture medium that contains cytokines and is free of stromal cells (see abstract). Cytokines are considered growth factors for hematopoietic cells. The cells propagated in the methods of Hoffman *et al.* are isolated from human iliac crests (see column 4, lines 36-43). The marrow cultures produced cells that are suspended (float in the medium) and non-adherent (see column 4, lines 66-67). The cells of Hoffman *et al.* are also treated with the growth factor c-kit ligand (see column 3, lines 4-8). If the cells respond to c-kit ligand it can be inferred that the cells express c-kit. Claims 55, 61, 62, 66, 67, 69, 70, 72, 74 and 75 read on the cells and methods of Hoffman *et al.*

Conclusion

Claims 55-78 are rejected. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katharine F. Davis whose telephone number is (703) 605-1195 with direct desktop RightFax (703) 746-5199. The examiner can normally be reached on Monday-Friday (8:30am-5:00pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Schwartzman can be reached on (703) 308-7307. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for

After Final communications. Any inquiry concerning the formalities of this application should be directed to Patent Analyst Dianiece Jacobs whose telephone number is (703) 305-3388. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Katharine F. Davis
July 26, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

Application No.: 09/635,370 File

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set by the Office communication to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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